



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

7d

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,958	05/02/2005	Helen Braven	ATLAS 8095 US	8800
39843	7590	06/14/2007		
BELL & ASSOCIATES 416 FUNSTON ST., SUITE 100 SAN FRANCISCO, CA 94118			EXAMINER POHNERT, STEVEN C	
			ART UNIT	PAPER NUMBER
			1634	
			MAIL DATE	DELIVERY MODE
			06/14/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/506,958	<b>Applicant(s)</b> BRAVEN ET AL.	
	<b>Examiner</b> Steven C. Pohnert	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-9, 11-60 and 63-108 is/are pending in the application.
- 4a) Of the above claim(s) 26-60, 63-90 and 106-108 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-25 and 91-105 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/13/2005</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. The application fails to comply with CFR 1.821(d), which states:

(d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, page 20 lines 32-33, contains a nucleic acid sequence. Applicant is required to check the rest of the disclosure for any other nucleic acid or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification must be amended to bring it into sequence compliance. **A response to this office action will be held non-compliant if the specification has not been amended to make it sequence compliant.**

### ***Election/Restrictions***

2. Applicant's election with traverse of Group I, claims 1-9, 11-25, 91, 92 and newly amended claims 93-105 in the reply filed on 3/16/2007 are acknowledged. The traversal is on the ground(s) that methods of detecting proteins by the use of oligonucleotide probes binding a specific protein and electronically determining information is substantially similar to the methods of detecting nucleic acids of group I. This is not found persuasive because the instant application is a 371, and thus falls under lack of unity practices. As stated in the restriction requirement the use of electrochemical labels to probe for nucleic acids (see Clinical Micro Sensors, Inc

Art Unit: 1634

(WO01/06016, Published January 25, 2001) under 102 rejection) were known at the time of filing and thus the groups lack a special technical feature over the prior art. The requirement is still deemed proper and is therefore made FINAL.

A first action on the merits of claims 1-9, 11-25 and 91-105 follows.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9, 11-25, 91-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 11-25, 91-105 are indefinite because they lack a positive active step relating back to the preamble. The preamble recites a method of probing a nucleic acid, however the last positive active step is drawn to electrochemically determining information relating to the electrochemical active marker. Therefore it is unclear as to whether the method is drawn to probing a nucleic acid or electrochemically determining information relating to the electrochemical active marker.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 11-18, 20-25, 91, 92, and 99-101 are rejected under 35 U.S.C. 102(b) as being anticipated by Clinical Micro Sensors, Inc (WO01/06016, Published January 25, 2001).

Clinical Micro Sensors is here after referred to as CMS.

With regards to claim 1, CMS et al teaches a method of detecting a nucleic acid by use of two probe labeled with electron transfer moieties (10 and 12) (electrochemically active marker) linked by a scissile linker (11) which comprises (1) at the top of figure 30. CMS further teaches the two probe linker complex (1) is provided condition in which it can hybridize to the target sequence (120) forming complex (6), the linker is then cleaved (or degraded). CMS further teaches the detection of both probes 10 and 11 by electron transfer (electrochemically), thus detecting the presence of the target nucleotide (bottom of figure 30).

With regards to claim 2, the method of CMS allows detection of target sequence 120, by electrochemical detection of probes 10 and 12 (see figure 30).

With regards to claim 3, CMS teaches the method allows for the quantifiable detection of the rate of generation of cleaved fragments or the amount of final products (see page 34, lines 8-18). As CMS teaches the use of specified amounts of probes, CMS thus inherently teaches the quantifiable detection of relative portions of degraded and non-degraded probes.

With regards to claims 11 and 12, CMS teaches the use of Invader<sup>™</sup> technology as a preferred embodiment. CMS teaches the use of an "invader primer and a signaling primer that has an overlapping sequence(see page 42, lines 8-11). CMS further

teaches that invader technology is based on structure specific polymerases that cleave nucleic acids in a site-specific manner (see page 42, lines 1-3). With regards to claim 12, CMS teaches the use of 5' thermostable nucleases (see page 42, line 16).

With regard to claim 13, CMS further teaches that invader technology is based on structure specific polymerases that cleave nucleic acids in a site-specific manner (see page 42, lines 1-3).

With regards to claims 14 and 15, CMS further teaches these polymerase/nuclease can be from Taq (see page 42, line 16).

With regards to claim 16, CMS teaches a new primer binds after cleavage (see page 42, line 19). CMS thus teaches a solution comprises a primer pair suitable for extension.

With regards to claim 17, CMS teaches PCR amplification using Taq polymerase by cycling in the preferred embodiment (see page 21, lines 16-20).

With regards to claim 18, CMS teaches the use of invader technology using two probes. Invader technology is based on hybridization of first oligonucleotide and a second oligonucleotide to a target sequence, with a non-complementary overlap that is cleaved by a nuclease (see page 42, lines 1-25). CMS further the ETM tagged tail is released in the cleavage by a nuclease that specifically recognizes the structure of the 2 probe target complex, the cleavage releasing the tail with an ETM tag (see page 42, lines 1-5 and lines 21-25). This cleavage shortens the oligonucleotide to which the ETM is attached.

With regards to claim 20, CMS teaches the detection of mutations, which are nucleic acid polymorphisms (see page 113, line 12).

With regards to claim 21, CMS teaches the detection of BRCA1, P53, APOE4 for the presymptomatic screening of patients. CMS thus teaches detection of allelic polymorphisms (see page 113, line 12).

With regards to claim 22, CMS teaches the probe array for use in sequencing by hybridization which would determine single nucleotide polymorphisms (see page 113, line 33).

With regards to claim 23, CMS teaches its method allows detection of  $10^6$  molecules (see page 114, line 35). CMS thus teaches the quantifiable detection of nucleic acid species.

With regards to claim 24, CMS teaches its method can be used for the detection of mRNA (see page 114, lines 18).

With regards to claim 25, CMS teaches the use of software directed microprocessor for the detection of electrochemical active species (figure 20A).

With regards to claim 91, CMS teaches in figure 32 the use of two oligonucleotide probes 10 and 12 with two different EMT probes 135 and 13.

With regards to claim 92, CMS teaches in figure 20 a-o, that two or labels can be distinguished by peaks on their voltametric traces.

With regards to claim 99, CMS teaches the use of voltammetry methods for detection (see page 105, line 10).

With regards to claim 100, CMS teaches the use of amperometry for detection (see page 105, line 10).

With regards to claim 101, CMS teaches the use of differential pulse voltammetry (see page 106, lines 25-26).

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 4-9 and 94-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kumar et al (US Patent 5,770,370 issued June 23, 1998) in view of Clinical Micro Sensors, Inc (WO01/06016, Published January 25, 2001).

Kumar et al teaches nuclease protection assays are a sensitive method for determining whether a nucleic acid sample contains a specific nucleic acid sequence or determining the amount of a nucleic acid sequence in a sample (see column 1, lines 23-30). Kumar et al teaches a nuclease protection assay is conducted by hybridizing a sample nucleic acid with a labeled probe nucleic acids (radioactive or fluorescent), followed by the addition of a nuclease that hydrolyses any single stranded DNA (see column 1, lines 25-30). Kumar teaches the use S1 nuclease, exonuclease VII, ribonuclease A, ribonuclease T, neurospora endonuclease in these protection assays (see column 2, lines 13-17).



Kumar does not teach the use of electrochemical labels or the detection of electrochemical labels.

However, Clinical Micro Sensors (CMS) teaches the use of electrochemical detection moieties (CMS calls ETMs) to as labels to detect nucleic acid sequences (see abstract). CMS further that ETMs allows amplification of signal resulting in sensitive assays (see page 54, lines 7-50).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the nuclease protection assay of Kumar, by use of CMS electrochemical detection labels in place of the fluorescent or radioactive labels. The ordinary artisan would be motivated to replace the labels of Kumar with the electrochemical labels of CMS, because CMS teaches they allow sensitive detection by signal amplification.

9. Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clinical Micro Sensors, Inc (WO01/06016, Published January 25, 2001) in view of Nikiforov et al (US Patent issued May 21, 1996).

CMS teaches the use of Invader<sup>tm</sup> technology as a preferred embodiment. CMS teaches the use of an invader primer and an ETM labeled signaling primer that has an overlapping sequence that does not hybridize (see page 42, lines 8-11). CMS teaches the use of 5' nucleases (see page 42, lime 16).

CMS does not teach the use T7 exonuclease.

However, Nikiforov et al teaches the use of T7 exonuclease in primer extension assays to generate single stranded nucleic acids (see abstract). Nikiforov et al teaches

that T7 exonuclease has the advantage over other nucleases that it has maximal activity in buffers suitable for DNA polymerase activity.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the CMS electrochemical Invader based nucleic acid detection method by use of the T7 exonuclease taught by Nikiforov, because Nikiforov teaches T7 exonuclease can be used in the same buffer that amplification.

10. Claims 102-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clinical Micro Sensors, Inc (WO01/06016, Published January 25, 2001) in view of Heller et al (US Patent 5,605,622, filed Issued February 25, 1997).

Clinical Micro Sensors is here after referred to as CMS.

CMS et al teaches a method of detecting a nucleic acid by use of two probes labeled with electron transfer moieties (10 and 12) linked by a scissile linker (11). CMS further teaches the two probe linker complex is hybridized to a target sequence, the linker is cleaved (or degraded). CMS further teaches the detection of both probes 10 and 11 by electron transfer, thus detecting the presence of the target nucleotide (bottom of figure 30). CMS teaches the uncleaved probes must be removed (see page 37, lines 25-30). The uncleaved probes of CMS are single stranded nucleic acids.

CMS does not teach the use of electrochemical technique utilizing selectively one or more electrodes functionally surrounded by permeable membrane that is permeable on the basis of charge, size, or hydrophobicity.

However, Heller et al teaches the use of permeation layers covering electrodes that allow solvent movement, while allowing exclusion based on size and charge (see column 11, lines 3-23; column 13, lines 30-55). Heller teaches the use of charge in the permeability layer he also inherently teaches the use of hydrophilic layers, as charge molecules are hydrophilic. Heller teaches the permeation layer functionally surrounding the electrode inhibits large proteins in the sample from binding the electrode, thus allowing the use of DC current (see column 11, lines 17-35). If the large proteins bound to the electrode, the large proteins would act as insulators, and cause a short circuit.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of CMS to include the use of a electrode with a selectively permeable membrane (permeation layer) of Heller, because Heller teaches the permeation layer allows the use of direct current without the insulating effects of large proteins binding to the electrode. The use of Heller's permeation layer would thus result in more accurate and sensitive assays.

11. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clinical Micro Sensors, Inc (WO01/06016, Published January 25, 2001) in view of Hall et al (US Patent 5,994,069 issued November 30, 1999).

Clinical Micro Sensors is here after referred to as CMS.

CMS et al teaches a method of detecting a nucleic acid by use of two probe labeled with electron transfer moieties (10 and 12) linked by a scissile linker (11). CMS further teaches the two probe linker complex is hybridized to a target sequence, the

Art Unit: 1634

linker is cleaved (or degraded). CMS further teaches the detection of both probes 10 and 11 by electron transfer, thus detecting the presence of the target nucleotide (bottom of figure 30). CMS further teaches the use of ETM with Invader technology (see column 42, lines 1-25).

CMS does not teach the use of a second recognition cassette that is labeled for detection of the cleavage reaction of a first partially hybridized complex.

However, Hall et al teaches a method of signal amplification using an invader probe, an unlabeled 1<sup>st</sup> probe, and a labeled second probe (see figure 96, and column 71 lines 45-52). Hall teaches the invader probe binds a first target sequence, while the 1<sup>st</sup> probe partially hybridizes the target and the unhybridized 5' tail of the 1<sup>st</sup> probe is released. The 5' tail of the 1<sup>st</sup> probe then hybridize a second target sequence, causing the 5' tail of the 2<sup>nd</sup> labeled probe to only partially hybridize to the second target sequence. Hall teaches the labeled 5' end of the second sequence is thus cleaved, released, and detected. The 2<sup>nd</sup> labeled probe and 2<sup>nd</sup> target are a recognition cassette.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improvement of the ETM invader method of CMS by use of Halls 2<sup>nd</sup> labeled probe and target. The ordinary artisan would be motivated to improve CMS method by use of Hall's 2<sup>nd</sup> labeled probe and target, because Hall teaches it amplifies the signal, resulting in a more sensitive assay. The combined teachings of CMS and Hall would result in a more sensitive electrochemical invader assay, than that taught by CMS.

### Summary

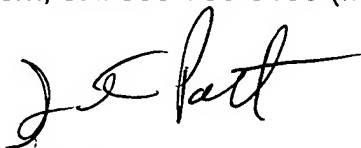
No claims are allowed over prior art cited.


### Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Steven Pohnert

  
JEANINE A. GOLDBERG  
PRIMARY EXAMINER  
6/8/07